

Maternal and fetal parameters including umbilical artery PI and fibrinogen/CRP ratio as predictive factors of perinatal outcome in women with HELLP syndrome

Matczyne i płodowe parametry uwzględniające indeks pulsacji tętnicy pępowinowej oraz wskaźnik fibrynogen/CRP jako czynniki predykcyjne wyników noworodkowych u kobiet z ciążą powikłaną wystąpieniem zespołu HELLP

Aleksandra Brucka-Kaczor¹, Piotr Woźniak², Ewelina Litwińska¹, Agnieszka Pięta-Dolińska¹, Przemysław Oszukowski¹

¹ Perinatology and Gynecology Department, Polish Mother's Memorial Hospital Research Institute, Łódź, Poland

² Specialist Gynecology and Obstetrics Outpatient Clinic, Polish Mother's Memorial Hospital Research Institute, Łódź, Poland

Abstract

Introduction: HELLP syndrome appears in approximately 0.2-1% of all pregnancies and is associated with increased maternal and fetal mortality and morbidity. It is diagnosed in cases when all three of the following criteria are present: 1) microangiopathic hemolytic anemia with abnormal blood smear, low serum haptoglobin and elevated LDH levels; 2) elevated ASPAT and ALAT (levels of both enzymes more than twice the upper limit of normal values), or bilirubin more than 1.2 mg/dl; 3) platelet count below 150x10⁹ L⁻¹. The etiopathogenesis of HELLP syndrome is associated with abnormal placentation in the first trimester, production of cellular active substances, and pathological response of the maternal organism. Objectives: The aim of the study was to establish maternal and fetal characteristics and perinatal outcome in HELLP syndrome. The examination protocol included comparison of maternal blood parameters, umbilical artery pulsatility index (UmbA PI) in relation to short-term neonatal outcomes.

Material and methods: Retrospective data analysis of patients hospitalized at the Perinatology and Gynecology Department, Polish Mother's Memorial Hospital Research Institute between 2009-2013, due to HELLP syndrome was conducted.

Results: None of the investigated maternal or fetal parameters correlated with the neonatal outcome.

Conclusions: Our study demonstrated that maternal parameters do not influence the perinatal outcome in women with HELLP syndrome. Moreover, UmbA PI and fibrinogen/CRP ratio do not correspond to neonatal parameters, either. Thus, none of the examined features can be used as a prognostic factor of the neonatal outcome. Further studies with large sample size are necessary but the rarity of this complication limits the possibility of research.

Key words: **HELLP syndrome / umbilical artery pulsatility index / fibrinogen / CRP ratio / perinatal outcome /**

Corresponding author:

Aleksandra Brucka-Kaczor
Perinatology and Gynecology Department, Polish Mother's Memorial Hospital Research Institute
93-339 Łódź, Rzgowska 281/289 Poland,
Tel: +48 422711083,
e-mail: alexbrucka@poczta.onet.pl

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Streszczenie

Wstęp: Zespół HELLP jest powikłaniem występującym z częstością około 0,2-1% ciąży. Związany jest z wysoką matczyną i płodową zachorowalnością i śmiertelnością. Zespół HELLP cechuje się jednoczesnym występowaniem triady objawów pod postacią: 1) mikroangiopatycznej anemii hemolitycznej z nieprawidłowym rozmażem krwi, niskim poziomem haptoglobiny i podwyższonym poziomem LDH; 2) podwyższonej dwukrotnie powyżej normy aktywności enzymów wątrobowych AspAT, AlAT lub stężenia bilirubiny powyżej 1,2 mg/dl; 3) małopłytkowości ($PLT < 150 \times 1009 L^{-1}$). Etiopatogeneza zespołu HELLP, uznawanego za ciężką postać stanu przedrzucawkowego, związana jest z nieprawidłową inwazją trofoblastu we wczesnych etapach ciąży.

Cel pracy: Celem pracy było określenie matczyńskich i płodowych parametrów oraz wyników perinatalnych w ciążach pacjentek powikłanych wystąpieniem zespołu HELLP. Protokół badania uwzględniał porównanie parametrów krwi matki, indeksu pulsacji tętnicy pępowinowej w powiązaniu z krótkoterminowymi wynikami noworodkowymi.

Materiał i metody: Przeprowadzono analizę retrospektywną danych pacjentek hospitalizowanych w Klinice Perinatologii i Ginekologii Instytutu Centrum Zdrowia Matki Polki w Łodzi w latach 2009-2013 z powodu wystąpienia objawów zespołu HELLP.

Wyniki: Żaden z ocenianych matczyńskich i płodowych parametrów nie korelował z wynikami noworodkowymi.

Wnioski: W badaniu nie stwierdzono związku między parametrami matczynymi a wynikami perinatalnymi wśród kobiet, których ciąża powikłana była wystąpieniem zespołu HELLP. Ponadto indeks pulsacji tętnicy pępowinowej i wskaźnik fibrynogen/CRP również nie korelował z wynikami noworodkowymi. Żaden z badanych parametrów nie może być stosowany jako czynnik prognostyczny wyników noworodkowych. Niezbędne są dalsze badania obejmujące duże populacje pacjentek. Jednakże rzadkość występowania tego powikłania ogranicza możliwość przeprowadzania takich analiz.

Słowa kluczowe: zespół HELLP / indeks pulsacji tętnicy pępowinowej /
/ wskaźnik fibrynogen / CRP / wyniki noworodkowe /

Introduction

In 1982, Weinstein described a group of obstetric patients with hemolysis (H), elevated liver enzymes (EL), and low platelet count (LP), and termed this entity 'the HELLP syndrome' [1]. Most of these patients suffered from mild hypertension and Weinstein considered the syndrome to be a form of severe preeclampsia. The patients had often been given a non-obstetric diagnosis before Weinstein's findings were announced, and therefore the treatment had frequently failed.

Every year, up to half a million mothers around the world lose their lives to pregnancy-related complications. Approximately 1 in every 6 of these deaths is the consequence of preeclampsia, eclampsia, HELLP syndrome, or any other form of hypertensive disorder of pregnancy [2, 3]. HELLP syndrome appears in about 0.2-1% of pregnancies [4], and is associated with increased risk of adverse outcomes for both, the mother and the fetus [1]. Signs of preeclampsia may be subtle or missing, but hypertension is present in most cases [4]. Early detection and precise diagnosis are essential for proper management. Maternal symptoms may be ambiguous and must be differentiated from a variety of medical disorders [5]. There are two main diagnostic definitions of HELLP syndrome. The Tennessee classification requires the manifestation of: 1) microangiopathic hemolytic anemia with abnormal blood smear, low serum haptoglobin and elevated LDH levels, 2) elevated ASPAT and ALAT (levels of both enzymes more than twice the upper limit of the normal values), or bilirubin more than 1.2 mg/dl and platelet count below $150 \times 1009 L^{-1}$. Incomplete syndrome ('ELLP') may be less severe. The Mississippi Triple-class classification grades the disorder according to platelet count [6].

HELLP syndrome is usually connected with hypertension (up to 80% of cases) or preeclampsia (PE) [7]. No coexistence of

hypertension or proteinuria is found in up to 15% of the affected patients [8]. The onset of HELLP and PE before 28 weeks of gestation accounts for about 20-30% of the cases, whereas 10-15% of women with HELLP syndrome develop the disease after delivery, what is usually more difficult to diagnose and treat.

HELLP and PE are the result of abnormal placentation in the first trimester [4,9]. Maternal symptoms in the majority of cases occur in the second half of pregnancy and are believed to be the consequence of the emission of products from a stressed placenta [9]. Fetal growth restriction is frequently a concomitant disorder in case of early onset HELLP or PE.

Delivery is the only effective treatment of HELLP syndrome identified so far. The corticosteroid therapy, apart from a single course for fetal lung maturation, is of unclear clinical value [5]. Maternal HELLP disorders disappear after delivery. However, the protracted disease course might be more severe.

Risk of HELLP syndrome among children and sisters of a woman who suffered from the disease is elevated [4]. Also, the affected women are in danger of developing HELLP in subsequent pregnancies (14-24%) [10, 11]. The common genetic reason for excessive risk of PE or HELLP remains to be elucidated. The combined effect of multiple gene variants, together with maternal and environmental factors, is a possible pathomechanism.

The impact of placental development on the risk of HELLP manifestation has long been recognized [12]. One of the theories of dysfunctional placentation is abnormal maternal immune response to the invading trophoblast [4]. The syncytiotrophoblast membrane and other cellular compartments composing the placental tissue demonstrate abnormal morphology or protein composition [4, 13].

Increased anti-angiogenic factor levels evoke maternal vascular endothelial dysfunction, which causes glomerular endothe-

liosis or hypertension in HELLP or PE [9, 14, 15]. Furthermore, trophoblast secretions enhance the inflammatory response in HELLP, together with coagulation activation [4, 16, 17].

The aim of our study was to ascertain the characteristics, clinical features and perinatal outcome in HELLP syndrome at a tertiary referral center. The examination protocol included comparison of maternal blood morphological and biochemical parameters, UmbA PI, and neonatal data.

Material and methods

Medical records of the pregnant women admitted for delivery to the Perinatology and Gynecology Department, Polish Mother's Memorial Hospital Research Institute between January 1, 2009, and December 31, 2013, were carefully reviewed retrospectively to check if their pregnancies were complicated by HELLP syndrome. Ten cases were found. The diagnosis of HELLP syndrome required the presence of all three of the following criteria: i) thrombocytopenia (<150.000 cells/L), ii) evidence of hepatic dysfunction (increased aspartate aminotransferase level >40 IU/L, increased alanine aminotransferase level >40 IU/L, or both, with increased lactate dehydrogenase [LDH] level >600 IU/L), iii) hemolysis (characteristic appearance of peripheral blood smear and serum lactate dehydrogenase [LDH] level >600 U/L or serum total bilirubin level >1.2 mg/dL), usually in association with hypertension or proteinuria considered to represent preeclampsia or eclampsia. Detailed evaluations of maternal and neonatal records for each patient in the database were accumulated. Charts were examined for standard demographic data, i.e. age, race, body mass index, gravidity, parity, and method of conception. Route of delivery, birth weight, range of blood pressure, laboratory values and umbilical artery Doppler measurements were assessed. Maternal history of chronic hypertension, other medical diseases, or previous preeclampsia was elicited. In addition, discharge time and major complications were documented.

Women currently using anticoagulants were excluded from the analysis. The key aim of the study was to specify whether the investigated variables were characterized by normal distribution. Therefore, Kolmogorov-Smirnov test with Lilliefors Significance Correction (K-S) and Shapiro-Wilk test were used. The p -value of <0.05 was considered statistically significant. In order to evaluate the correlation between values, Pearson's index of linear correlation was used, r_{xy} . This index is a dimensionless quantity, which includes values from the range of -1 to 1. Pearson's index is a measure of linear relationship between two measurable values. While evaluating Pearson's index of linear correlation, it is important to keep in mind that if the value of the index equals 0, it does not always determine lack of relationship but only lack of linear relationship. If lack of relationship was stated, Spearman's correlation index of ranges is used. Spearman's correlation index of ranges was also used for non-normally distributed variables. In this case, the assumption of normality of the distribution of each variables is not necessary.

Results

During the study period, 10 patients were treated for HELLP syndrome at the Department of Perinatology and Gynecology, Polish Mother's Memorial Hospital. Of the 5513 deliveries that occurred during that time, the 10 patients with HELLP syndrome represented 0.18% of the entire population. A total of 70% of

the study group presented with symptoms of pregnancy-induced hypertension before HELLP was diagnosed, 60% of the patients were diagnosed with preeclampsia, 30% with severe preeclampsia, and eclampsia was identified in 1 patient (10%).

Maternal demographic and clinical characteristics, as well as fetal data, i.e. birth weight, Apgar scores, and arterial umbilical blood pH values, are shown in Tables I and II.

General characteristics of the examined group included patient age, body mass index (BMI), gravidity, and gestational age. Mean patient age was 29.5 ± 5.6 years, what emphasizes mild differentiation of the feature. The majority of the women were nulliparous (70%). Average BMI was 29.7 ± 5.53 , what highlights moderate disparity of the quality as well. BMI of half of the group did not exceed 31.5. None of the women suffered from glucose intolerance, diabetes or other metabolic disorders. One patient was diagnosed with factor V Leiden mutation and 1 was treated for hypothyreosis.

Prenatal diagnostics did not reveal any congenital malformations of the fetuses. During hospitalization, the fetuses were monitored by the use of non-stress test and fetal Doppler study of the umbilical artery, vein and ductus venosus flow.

Mean fetal gestational age was 28.9 ± 3.36 weeks, and 50% of the fetuses were born before 28 weeks. Regular birth weight was 961.5 ± 464.3 g, with average Apgar score of 5.4 ± 2.99 (1-8) and pH value of 7.25 ± 0.05 (7.18-7.34).

During the diagnostics-therapeutic process, Dexamethasone was administered in two doses (12mg intravenously every 24 hours) in 90% of the patients. One dose of corticosteroids was administered 5 hours before Cesarean section due to severe preeclampsia in only 1 patient. There is no standard protocol of corticosteroid administration in case of low platelet treatment in patients with HELLP syndrome.

Table II contains details of maternal laboratory findings before delivery, and prenatal findings such as UmbA PI, and neonatal characteristics. The main target was to detect any correlations between maternal blood CRP/fibrinogen ratio or any other maternal blood test result, fetal UmbA PI, and neonatal characteristics such as: Apgar score, umbilical artery blood pH, or birth weight (Table III) among patients with HELLP syndrome. No significant relationship was observed between the investigated characteristics. Furthermore, it was estimated by the ANOVA protocol analysis that the neonatal mortality rate was independent of any of the assessed features (data not included).

A total of 70% of the patients delivered by Cesarean section: 3 out of 7 because of previous Cesarean section and the rest due to rapid deterioration of laboratory blood and biochemical tests, and 30% of women delivered vaginally. Two patients were reoperated because of symptoms of intraperitoneal bleeding one day after Cesarean section (one of them was diagnosed with DIC formerly, the other one demonstrated severe anemia). None of them required radical treatment such as hysterectomy. All women recovered but 3 neonates died because of prematurity consequences (30%).

Discussion

Despite the fact that diagnostic criteria were accepted about thirty years ago, HELLP syndrome remains difficult to recognize and successful diagnostic-therapeutic process remains challenging [18].

Table I. Demographic characteristics of gravidas with HELLP syndrome.

Characteristics	Mean	SD	Median	x_{\min}	x_{\max}
Age (years)	29.5	5.6	28.5	22	37
BMI (kg/m ²)	29.7	5.53	31.5	21.4	36.4
Gestational age (weeks)	28.9	3.63	28	25	36

Table II. Clinical characteristics and results of Kolmogorov-Smirnov normality test with Lilliefors' Significance Correction.

Variables	Number of observations	Mean value	SD	Median value	x_{\min}	x_{\max}	Test K-S value
UmbA PI	10	1.33	0.26	1.35	0.865	1.68	0.147
HGB (g/dl)	10	11.39	1.58	12.45	9.30	13.90	0.217
CRP (mg/dl)	7	5.15	4.73	3.04	2.25	15.60	0.327
PLT (10 ³ /μl)	10	96.55	35.81	99.5	38.5	140.0	0.117
APTT(s)	10	31.67	3.84	32.05	26.3	39.7	0.163
Fibrinogen (g/L)	10	3.87	1.69	4.01	0.6	6.10	0.152
Fibrinogen/CRP ratio	7	1.25	0.68	1.26	0.17	2.08	0.151
INR	10	1.06	0.37	0.92	0.8	1.80	0.368
D-dimers (ng/mL)	10	11341.7	11313.3	5328.0	1430.0	31012.0	0.270
ASPAT (IU/L)	10	228.9	141.1	183.0	76.0	455.0	0.222
ALAT (IU/L)	10	173.9	74.75	186.0	59.0	283.0	0.147
LDH (IU/L)	10	1701.7	1574.6	1208.0	762.0	5979.0	0.358
Serum total protein value (g/dl)	10	4.14	0.87	4.40	2.0	4.90	0.227
Serum total bilirubin value (mg/dl)	10	1.67	1.64	1.25	0.2	6.0	0.320
Birth weight (g)	10	961.5	464.3	875.0	350.0	1810.0	0.160
APGAR score	10	5.40	2.99	5.50	1.00	10.0	0.172
Umbilical artery blood pH	10	7.25	0.05	7.24	7.18	7.34	0.215

We analyzed maternal, fetal and neonatal factors in women affected by HELLP syndrome, aiming to find a correlation between them and maternal early puerperium complications and/or perinatal outcome: birth weight, umbilical artery blood pH, and Apgar score.

According to the literature, HELLP syndrome tends to affect multiparous women over 25 years of age. In our cohort, average maternal age was 29.5 years. In contrast to the general data, we observed the disease affects primigravidas more often (70%), what is consistent with the results of Hupuczi P et al. [2, 18, 19].

HELLP syndrome has been known to be a variant presentation of severe preeclampsia [20]. The exact etiology of preeclampsia remains to be fully elucidated but impaired placental implantation with abnormal trophoblastic invasion of the uterine vessels plays a major pathophysiologic role in the development of preeclampsia and HELLP syndrome [21].

Our findings on frequency of preeclampsia (60%), severe preeclampsia (30%), and eclampsia (10%) are consistent with

statistical reports in the literature. None of our patients developed the most rare form of HELLP syndrome appearing in puerperium [20].

The main objective of our study was to monitor perinatal outcome among women with HELLP syndrome using maternal demographic characteristics, laboratory findings and fetal parameters, as presented in Table II. We analyzed maternal and fetal factors and related them to perinatal outcome, including birth weight, umbilical artery pH, Apgar score at 5 minutes, and mortality. To the best of our knowledge, data on the topic are scant [21-23], with most studies focusing on maternal rather than neonatal outcomes [22, 24, 25].

Our review did not disclose any associations between maternal age or gravidity and the perinatal outcome, including mortality (Table III). Maternal laboratory findings, routinely checked to monitor patients with HELLP syndrome, were not independent risk factors for adverse fetal outcomes. Our findings are consistent with data collected by Guzel AI et al., who found no

Table III. Statistical analysis of correlations between maternal, fetal and neonatal parameters – results

	UmbA PI	Umbilical artery blood pH	Gestational age (weeks)	Birth weight (g)	APGAR score
HGB (g/dl)	0.467 ^{S*} (*P=0.174)	0.474 ^S (P=0.166)	0.099 ^{P*} (P=0.831)	0.015 ^P (P=0.974)	-0.242 ^S (P=0.601)
CRP (mg/dl)	-0.126 ^S (P=0.788)	0.143 ^S (P=0.759)	-0.072 ^S (P=0.878)	0.285 ^S (P=0.534)	0.043 ^S (P=0.928)
PLT (10 ³ /ml)	-0.639 ^P (P=0.122)	-0.134 ^S (P=0.713)	0.528 ^P (P=0.223)	0.529 ^P (P=0.223)	0.502 ^P (P=0.250)
APTT (s)	-0.332 ^P (P=0.466)	-0.528 ^S (P=0.116)	0.821^S (P=0.024)	0.734 ^P (P=0.060)	0.624 ^S (P=0.215)
Fibrinogen (g/L)	0.674 ^P (P=0.097)	0.103 ^S (P=0.776)	0.430 ^P (P=0.336)	0.365 ^P (P=0.420)	0.032 ^P (P=0.946)
Fibrinogen/CRP	0.152 ^S (P=0.629)	0.115 ^S (P=0.792)	0.312 ^S (P=0.529)	0.214 ^S (P=0.584)	0.063 ^S (P=0.897)
D-dimers (ng/ml)	0.176 ^S (P=0.627)	0.267 ^S (P=0.455)	-0.530 ^S (P=0.114)	-0.600 ^S (P=0.069)	-0.385 ^S (P=0.271)
ASPAT (IU/L)	0.248 ^S (P=0.489)	-0.437 ^S (P=0.206)	-0.195 ^S (P=0.589)	-0.297 ^S (P=0.405)	-0.422 ^S (P=0.244)
ALAT (IU/L)	0.339 ^P (P=0.456)	-0.596 ^S (P=0.069)	0.233 ^P (P=0.615)	0.123 ^P (P=0.792)	0.146 ^P (P=0.755)
LDH (IU/L)	0.042 ^S (P=0.907)	0.073 ^S (P=0.841)	-0.384 ^S (P=0.273)	-0.224 ^S (P=0.533)	0.061 ^S (P=0.866)
Serum total protein value (g/dl)	0.128 ^S (P=0.724)	0.602 ^S (P=0.065)	-0.012 ^S (P=0.973)	0.134 ^S (P=0.711)	0.196 ^S (P=0.585)
Serum total bilirubin value (mg/dl)	0.253 ^S (P=0.584)	-0.259 ^S (P=0.470)	-0.446 ^S (P=0.196)	-0.328 ^S (P=0.354)	-0.337 ^S (P=0.340)

*P – Pearson's correlation coefficient; ^S – Spearman's rank correlation coefficient; p<0.05 – statistically significant

correlation between neonatal characteristics (body weight, Apgar score, umbilical artery pH or mortality) and maternal records [22]. Erdemoglu M et al., also did not reveal any correlations between hematological or biochemical maternal parameters and perinatal complications [18].

HELLP-related perinatal mortality has been described in other studies. Haram et al., determined the perinatal mortality rate to decrease with an increase in gestational age and/or fetal birth weight [26]. Liu et al., reported the perinatal mortality rate of 22.6%, with no significant differences resulting from coexisting preeclampsia [27]. Gul et al., investigated perinatal outcomes in patients with severe preeclampsia-eclampsia, with and without HELLP syndrome, and proved that HELLP is an independent risk factor of perinatal mortality. In their study, perinatal mortality rate was 34% for fetuses at 32 weeks of gestation and 8% at >32 weeks of gestation [28]. These findings are similar to ours, and to reports by Guzel AI et al. In our analysis, gestational age and birth weight were the highest risk factors for perinatal mortality. Perinatal mortality in HELLP syndrome has been estimated at 7.4-34%, with the incidence depending on gestational age at the onset of complications [26]. The pathomechanism of HELLP-induced perinatal mortality remains to be fully elucidated but it probably derives from impaired placentation and adverse maternal immune response to pregnancy [29, 30]. Martin et al., found HELLP syndrome to be associated with adverse perinatal outcome, including neonatal death, in cases with lower platelet count and higher LDH levels [31].

In our study, 3 cases of neonatal death were noted. All of them appeared as the effect of pregnancies complicated by pre-eclampsia or eclampsia, with simultaneous level of PLT <100 10³/μl and LDH >1200 ng/ml. However, statistical analysis did not reveal any relationship between the parameters, as in the study by Martin [31].

As for uteroplacental abnormality being the main pathological event in cases of pregnancy-related hypertensive disorders, alteration in UmbA Doppler velocimetry could be expected. Various studies showed that in pregnancies with uteroplacental insufficiency, UmbA Doppler velocimetry or pulsatility index (PI) can detect those at high risk for adverse neonatal outcome [21, 32, 33]. In our investigation, no significant correlations between UmbA PI and gestation age, Apgar score, birth weight, umbilical artery pH, or perinatal mortality were found. It is contrary to the reports of Simsek Y et al., who found abnormal UmbA Doppler values to correlate with perinatal mortality, neonatal intensive care unit treatment, lower birth weight, and younger gestation age [21]. These authors concluded that abnormal patterns of UmbA Doppler study are independent prognostic factors for neonatal outcome in patients with HELLP syndrome.

Blood fibrinogen and CRP level are among the factors used for monitoring patients with HELLP syndrome. However, since these proteins are acute phase reactants, they are not objective parameters. Kim et al., as well as Windsperger et al., proved the utility of monitoring the fibrinogen/CRP ratio [23, 33]. Moreover, Windsperger observed a significant correlation of the fibrinogen/

CRP ratio with the perinatal outcome [23]. In our study, we examined the correspondence of the fibrinogen/CRP ratio to all of the above mentioned maternal, fetal and neonatal factors. However, we did not reveal any statistically significant correlations between them.

Conclusions

Our study demonstrated that maternal parameters such as age, gravidity, or laboratory findings do not affect the perinatal outcome of infants born to women with HELLP syndrome. Moreover, UmbA PI and fibrinogen/CRP ratio do not correspond with neonatal parameters, either. None of the monitored factors can be used as a prognostic feature of neonatal outcome. Prematurity and associated parameters of low gestational age, low birth weight, and low Apgar score increase the risk for adverse perinatal outcome. A relatively small sample size was the main limitation of our study. It is necessary to investigate more cases with HELLP syndrome to draw conclusions with more certainty.

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1. Aleksandra Brucka-Kaczor – autor koncepcji i założeń pracy, przygotowanie manuskryptu i piśmiennictwa – autor zgłaszający i odpowiedzialny za manuskrypt.
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